DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute on Aging
Biomedical Research Center
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To: ABCC Review Committee

From: Irving W. Wainer, PhD, DHC
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It is my pleasure to write to you in reference to your review of the Advanced Biomedical Computing Center. I began working with ABCC in 2003, in particular Sarangan Ravichandran and Jack Collins. At that time, my group was beginning to computationally model ligand protein interactions and we were looking for some expert advice on how to proceed. We were fortunate to meet Ravi and Jack and to begin a very fruitful collaboration with them. Over the 7 years this collaboration has produced 5 published manuscripts in top international journals {see below} and two additional papers are in preparation. What is clear to me is that the ABCC is an intellectually vibrant organization that conducts state-of-the-art research. It is also an organization that effectively trains and motivates students.

The educational expertise of the colleagues in the ABCC was demonstrated during the initial stages of our collaboration. The project involved the computational modeling of the interaction of non-competitive inhibitors with the alpha3beta4 nicotinic acetylcholine receptor and was part of the postdoctoral research of Krzysztof Jozwiak. Krzysztof worked closely with Ravi and Jack and learned the computational methods used at ABCC. This collaboration produced 3 manuscripts {#1, 2 and 4} and help Krzysztof develop an independent and highly successful research program. He now heads the Laboratory of Drug-Receptor Interactions in the Department of Chemistry of the Medical University of Lublin where he continues to utilize the knowledge he gained at the ABCC.

Our laboratory has also collaborated with the ABCC in the development of new pharmacophore models describing the stereoselective binding of substrates to the human organic cation transporter (hOCT1), both the native and single nucleotide polymorphs (SNPs) of the transporter {#3 and 5}. These projects have addressed some key issues in the development of pharamcophore models of substrate-transporter interactions and also represent significant steps towards the development of *in silico* screens for use in drug development.

In our current collaboration, we have explored the subtle differences in the molecular structures of the stereoisomers of the anti-cancer agent ifosfamide. The computational and experimental data from this study have indicated that the stereoisomers are not enantiomers, as has been previously thought, but are diastereomers. While enantiomers have the same physicochemical properties, diastereomers do not. This observation was the direct result of the computational studies carried out at the ABCC and will produce a reevaluation of the metabolic transformation, pharmacological fate and clinical efficacy of ifosfamide.

I value my interactions with the ABCC and look forward to a continuing this very successful collaboration. In my opinion the center is a valuable asset for the NCI and I support their activities without reservations.

Sincerely,

Irving W. Wainer, PhD, DHC
Senior Investigator
Laboratory for Clinical Investigation
National Institute on Aging/NIH

Joint Publications ABCC/NIA

1. Jozwiak, K., Ravichandran, S., Collins, J.R. and Wainer, I.W.: The interaction of non-competitive inhibitors with the alpha3beta4 nicotinic acetylcholine receptor investigated by affinity chromatography, QSAR and molecular docking. J. Med. Chem. 47: 4008-4021, 2004.

2. Jozwiak, K., Moaddel, R., Yamaguchi, R., Ravichandran, S., Collins, J.R. and Wainer, I.W.: Qualitative assessment of IC_{50} values of inhibitors of the neuronal nicotinic acetylcholine receptor using a single chromatographic experiment and multivariate cluster analysis. J. Chromatogr. B., 819:169-174, 2005.

3. Moaddel, R., Ravichandran, S., Bighi, F., Yamaguchi, R., Wainer, I.W.: Pharmacophore modeling of stereoselective binding to the human organic cation transporter (hOCT1), Br. J. Pharmacol. 151: 1305-1314, 2007

4. Jozwiak, K., Moaddel, R., Ravichandran, S., Plazinska, A., Joanna Kozak, J., Sharvil Patel, S., Rika Yamaguchi, R., Wainer, I.W.: Exploring Enantiospecific Ligand-Protein Interactions Using Cellular Membrane Affinity Chromatography: Chiral Recognition as a Dynamic Process, J. Chromatogr. B. 875:200-207, 2008.

5. Moaddel, R., Bighi, F., Yamaguchi, R., Patel, S., Ravichandran, S., Wainer, I.W.: Stereoselective binding of chiral ligands to single nucleotide polymorphs (SNPs) of the human organic cation transporter-1 determined using cellular membrane affinity chromatography. Anal. Biochem., doi:10.1016/j.ab.2010.02.034